REMARKS/ARGUMENTS

Status of the claims

Claims 1, 3, 5, 11, and 13 are pending. No new matter is added.

Interview

Applicants appreciate the opportunity to discuss the outstanding rejections with Examiner Bao and her supervisor on April 14, 2010.

Rejection under 35 USC § 112, first paragraph – Written Description

The Examiner has rejected claims 1 and 5 as allegedly lacking written description. According to the Examiner, the claims are directed to a genus reading on "astronomic numbers of polypeptide variants of SEQ ID NO:2." The Examiner additionally asserts that the specification only teaches use of SEQ ID NO:2 for inducing a neutralizing antibody.

As an initial matter, the specification *does not teach* use of the Type I FIPV N protein to induce neutralizing antibody. As explained in detail below for the obviousness argument, neutralizing antibodies are very undesirable, as such antibodies risk an enhanced FIPV infection (*see, e.g.*, page 3, lines 23-27 of the specification). See also Table 2 on page 44, which shows that the vaccination *did not* stimulate an appreciable antibody response.

Applicants also respectfully disagree that the claims describe an astronomical number of polypeptide variants. Claim 1 describes polypeptides with 1-15 amino acid variations, or 95% or higher identity to SEQ ID NO:2, that immunologically stimulate immunocompetent cells. Note that SEQ ID NO:2 is 377 amino acids in length, so that 15 amino acid variations will have at least 96.1% identity to SEQ ID NO:2.

To meet the written description requirement, the specification must convey with reasonable clarity *to one of skill in the art* that the inventors were in possession of the claimed invention (*see* MPEP 2163.02). The written description requirement for a claimed genus may be satisfied by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed

correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Polypeptides within 95% identity to a given sequence are generally considered allowable, especially where the function of the polypeptide is familiar in the art.

Applicants analogize immunogenic polypeptides to antibodies, as both are considered familiar in the art. The 2008 Written Description Training Materials issued by the USPTO provide several examples of the written description analysis. Example 13 discusses a claim to an antibody specific for a disclosed protein, and demonstrates the importance of the level of skill in the art to the analysis. The Example explains that the claim meets the written description requirement, despite the fact that the specification discloses nothing about the structure of the claimed antibody. This is because antibodies and the antigen-binding function of antibodies are well-known in the art. The Technical Note in Example 13 explains that antibodies can be reliably generated. The analysis states that selection of functional antibodies is routine. Thus, because of the routine, familiar nature of the claimed subject matter, an antibody can be claimed with very little description.

Here, the recited polypeptide variants of SEQ ID NO:2 are immunogenic. Variants of an immunogenic polypeptide that retain immunogenicity are familiar in the art. One of skill in the art will readily recognize that the immunogenicity of a particular polypeptide rarely requires the entire, residue-by-residue sequence to remain unchanged. Immunogenic activity is generally retained despite minor modification. As explained below, minor variants of SEQ ID NO:2 can be reliably generated, and the immunogenic activity of a variant polypeptide can be tested using routine methods.

The present disclosure demonstrates successful use of the polypeptide of SEQ ID NO:2 as a vaccine (*see* section starting on page 41, line 32). Pages 11-15 of the specification demonstrate that the inventors considered similar use of variants of SEQ ID NO:2 to be part of the invention. The section explains that highly homologous proteins have similar immunological characteristics, and that the protein used in the vaccine need not include the entire structure of the full length antigen protein as long as it can immunologically stimulate immunocompetent cells. Epitopes, and epitope determination methods, are described on page 13.

As noted above, it is routine in the art to introduce slight variations to a protein sequence that has been found to be immunogenic in order to optimize the effect on cellular immunity, or to minimize undesired effects. The specification explains to one of skill that variations can be introduced to the immunostimulating protein of SEQ ID NO:2, and compared for immunogenic effect. Page 15 describes routine methods of determining cellular immunity, such as CTL assays.

Finally, Applicants note that claim 13, which recites an immunostimulating fragment having 45 or more continuous amino acids of SEQ ID NO:2, is not included in the rejection. The acceptance of claim 13 indicates that the immunostimulatory activity of a given polypeptide is considered familiar and sufficiently described to those of skill in the art.

Given these disclosures, and the level of skill in the art, one of skill would reasonably understand that the inventors were fully in possession of the claimed vaccines to provide immunity against FIVP. Accordingly, Applicants respectfully request withdrawal of the rejection under the first paragraph of 35 USC § 112 for written description.

Rejection under 35 USC § 103

The Examiner has rejected claims 1, 3, 5, 11, and 13 as allegedly obvious over Wasmoen (US Patent No. 5770211) in view of Motokawa (*Microbiol. Immunol.* 40:425-433 (1996)) and Duphar (EP0411684).

Wasmoen teaches a live raccoon poxvirus vaccine encoding an N protein from a *Type II* FIPV. Motokawa teaches the sequence of SEQ ID NO:2 from the present application, *i.e.*, an N protein from a *Type I* FIPV. Motokawa ***does not*** suggest use of the Type I N protein for a FIPV vaccine. Duphar describes the cloning of genes encoding the M or N protein from a *Type II* FIPV and proposes that a vaccine can be designed from these antigens. While Duphar acknowledges that a past attempts at designing a vaccine for FIPV have been unsuccessful, Duphar does not provide details about the proposed vaccine, or show evidence that it would work.

Interview

During the Interview, Applicants explained that the present invention is directed to a protein vaccine based on the N protein from a ***Type I*** FIPV, not a Type II FIPV, as disclosed in Wasmoen and Duphar. The Type I N protein has a different immunogenicity than the N protein from a Type II FIPV.

Applicants reviewed the evidence submitted in previous responses.

- Use of the Type I N protein for a vaccine presents a technical challenge. The specification explains that Type I FIPV proliferates slowly and is less pathogenic than Type II FIPV, leading to difficulties in production. In addition, Type I is less immunogenic than the Type II FIPV (see specification, page 6, line 9-21). Despite the fact that Type I FIPV causes more than 70% of FIPV cases, the specification explains that an effective vaccine utilizing Type I N protein had not been reported (*see* page 6, lines 9-21). One of skill would therefore not have a reasonable expectation of success in using the type I N protein as the basis for a vaccine.
- German, published after Wasmoen, and originally submitted with the April 13, 2009 response, describes the failure of others to design a Type I N protein vaccine against FIPV, or indeed, *any* vaccine against FIPV. German provides additional evidence of a long-felt need and failure of others in designing an effective vaccine against Type I FIPV.
- Horzinek was also published after Wasmoen, and originally submitted with the April 13, 2009 response. Horzinek also describes the failure of others to design an effective FIPV vaccine. Dr. Horzinek's commentary then describes the results disclosed in Hohdatsu *et al.* (2003) *Veterinary Microbiology* 97:31-44, which represents the post-filing publication from the inventors describing the present invention. Dr. Horzinek remarks that the survival rate of 75% achieved with the present vaccine is very high for this kind of experiment. Thus, Horzinek demonstrates that the claimed vaccine compositions are surprisingly effective.

- Further evidence of surprising results is found in the specification. The vaccine designed from *Type I* N protein conferred protection from challenge with *Type II* FIPV (*see* page 45, lines 10-30 and page 52, lines 10-30).

Cited art

The Examiner states that Wasmoen teaches successful immunization using a DNA vaccine encoding an FIPV N protein (*see* Office Action, paragraph 15). Applicants maintain that Wasmoen teaches a DNA vaccine encoding a Type II N protein and would not provide one of skill with a reasonable expectation of success in designing an FIPV vaccine comprising a Type I N protein, as claimed here.

First, Wasmoen teaches use of a Type II FIPV N protein, which is distinct from the present Type I FIPV N protein. As explained above, the Type I FIPV presents a greater technical challenge than Type II FIPV.

Second, while Wasmoen reports successful use of a DNA vaccine encoding Type II FIPV N protein, the results described by Wasmoen are not widely acknowledged in later reports in the field. Neither German nor Horzinek cite the Wasmoen patent or the corresponding *Adv Exp Med Biol* article. However, both references spotlight the continuing need for an effective vaccine for FIPV. The implication is that the FIPV vaccine reported by Wasmoen was not adopted in the field.

Third, the vaccine design and immunization procedure disclosed by Wasmoen are different than those presented in the present specification. Wasmoen discloses a DNA-based vaccine, which is distinct from the protein-based vaccine recited in the present claims. During the Interview, it was alleged that Wasmoen describes use of the N protein in the vaccine composition. However, the only mention of a vaccine comprising a protein component is found in col. 4, lines 31-43 of Wasmoen. This section discusses addition of an antigen or peptide from a *different virus* (*i.e.*, not FIPV) in combination with the disclosed DNA vaccine. Thus, Wasmoen does not provide any teaching regarding use of an FIPV N protein in a vaccine.

In addition, the results described in Wasmoen do not demonstrate the effect of the vaccine alone. Prior to challenge with FIPV, Wasmoen discloses administration of a *different virus*, Feline Enteric Coronavirus to sensitize the cats (Wasmoen, col. 8, line 63- col. 9, line 2).

In contrast, the presently disclosed results show that the claimed vaccine is sufficient for effective protection.

Applicants note that although Duphar proposes use of a Type II FIPV N protein as a vaccine (col. 2, lines 27-33), this reference does *not* disclose actual use of such a vaccine. Considering the known lack of success with previous FIPV vaccines, Duphar would not provide one of skill with a reasonable expectation of success using an Type II N protein vaccine, not to mention a Type I protein, as claimed here.

No reasonable expectation of success

MPEP 2143.02 confirms that a determination of obviousness requires a reasonable expectation of success, and some measure of predictability. The *KSR* Court emphasized the importance of predictability, and described obviousness as a combination of known elements or known methods that yield predictable results.

Given the difficulty in FIPV vaccines, the success of the present invention was not predictable. The cited references would not provide one of skill with a reasonable expectation of success using a vaccine comprising an N protein from Type I FIPV. The specification explains that vaccination against FIPV can expose the cat to more severe infection (*see* page 4, lines 1-8). This phenomenon, referred to in the art as Antibody Dependent Enhancement (ADE), is also described in Wasmoen (col. 1, lines 33-44), Duphar (col. 2, lines 1-7), and German (page 119, col. 2). One of skill recognized, therefore, that immune responses that favor an antibody response can actually exacerbate rather than prevent disease.

Thus, one challenge facing the art at the time of the invention was to design a FIPV vaccine that promotes cellular immunity (mediated by T cells) instead of humoral immunity (mediated by antibodies). To this end, it was generally known at the time of the invention that protein antigens tend to stimulate a humoral, antibody response, while viral infection tends to stimulate a cellular immune response. Applicants submit as evidence **Exhibit A**, Figure 7.28 from Janeway and Travers, Immunobiology 1994 edition. The left panel shows activation of cytotoxic T cells by viral infection. The right panel shows that a peptide antigen (in this case, a bacterial toxin) causes an antibody response.

Given this general knowledge, those of skill, concerned about ADE, would not reasonably expect a vaccine that tends to induce an antibody response would be useful for FIPV.

Secondary considerations

MPEP 2145 explains that the Office must consider evidence of secondary considerations in making a determination of obviousness. The teaching of the art must be considered in its entirety (*see also* MPEP 2141.02 VI)

The cited art, as well as reports published after the cited references, provide considerable evidence of secondary considerations. The present invention fulfils a long-felt need, where others had failed, and is surprisingly effective.

Duphar explains that an active vaccine against FIPV had not been found (col. 1, lines 49-50). This is confirmed by the Background in Wasmoen. Several years later, German explains that attempts at developing vaccines to FIPV had been largely unsuccessful (page 119, col. 1). Horzinek explains that FIPV vaccine development had been stagnant, despite many efforts (page 50, col. 2).

Horzinek, however, ends on a hopeful note after reviewing the results of the present invention ("Coronavirology has never looked better."). As explained above, Dr. Horzinek remarks that the survival rate of 75% is very high.

The present invention provides the additional surprising result of effectively protecting cats against a challenge from a *Type II* FIPV (*see* page 45, lines 10-30 and page 52, lines 10-30).

In addition, despite the known likelihood of promoting an undesirable antibody response using a protein-based vaccine, the specification shows that the Type I N protein vaccine did not stimulate appreciable antibody production (*see, e.g.*, Table 2, page 44). Surprisingly, the protein-based vaccine instead stimulated protective, cellular immunity (page 44, line 19 - page 45, line 7).

In summary, the cited references would not provide one of skill with a reasonable expectation of success using a vaccine comprising the N protein from Type I FIPV. The art discloses different vaccine compositions, and the evidence showing these compositions are

sufficient for protection from FIPV is lacking. In contrast, despite many unsuccessful attempts in the art, the presently claimed vaccine presents surprising efficacy, and is sufficient to mount a protective immune response in cats. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 USC § 103.

Rejection under 35 USC § 112, first paragraph – Enablement

The Examiner has rejected claims 1, 3, 5, 11, and 13 as allegedly lacking enablement. According to the Examiner, the specification is only enabling for a vaccine comprising an N protein from Type II IFPV (sic) of SEQ ID NO:2, L80/ aluminum hydroxide adjuvant, and a three dose immunization schedule (*see* Office Action, paragraph 19).

This rejection was discussed during the Interview. Applicants generally understood that the adjuvant and dosing schedule aspects would be reconsidered.

The standard for enablement is based on whether one of skill in the art at the time of the invention would be able to make and use the claimed invention without undue experimentation. The standard applied by the Examiner, however, would require Applicants to disclose *in vivo* data showing every permutation of N protein variant, adjuvant, and dosing schedule. This standard ignores the well-established aspects vaccine administration at the time of filing.

In addition, it should be immediately apparent that an invention can not be both obvious and non-enabled. To be obvious, the prior art, *even without the benefit of an applicant's disclosure*, must teach one of skill how to practice the invention. To not be enabled, the application, in combination with the prior art, must ***not*** sufficiently teach one of skill how to practice the invention. The legal relationship between obviousness and enablement is well established. To render an invention "obvious" the prior art as a whole (*i.e.*, all of the references and knowledge in the prior art) "must enable one skilled in the art to make and use the apparatus or method." *See Beckman Instruments Inc. v. LKB Produkter AB*, 13 USPQ2d 1301, 1304 (Fed. Cir. 1989). On the other hand, for enablement purposes, an application is considered for what it teaches, *in combination with the knowledge in the art.*

The elements of the enablement rejection, *i.e.*, the identity of the polypeptide and adjuvant used for the vaccine composition, and the dosage schedule, are considered obvious in the rejection under 35 USC § 103, addressed above. According to the obviousness rejection, such elements would be considered obvious ***without*** the present specification. Yet according to the enablement rejection, the specification ***lacks*** sufficient information to allow one of skill to make or use the claimed invention.

As explained above for the written description rejection, the specification and the knowledge in the art provide sufficient information for one of skill to design an immunogenic variant of SEQ ID NO:2. One of skill would readily be able to make small variations to the sequence of SEQ ID NO:2 and determine if these variants were sufficient to elicit a cellular immune response (again, see page 15 of the specification).

Adjuvants are well-known in the art, and described in the specification (*see, e.g.*, page 20, line 21 to page 21, line 18). Use of a vaccine according to the present claims would not require undue experimentation of one of skill in the art. One of skill could readily substitute various adjuvants and test the resulting vaccines in parallel without undue experimentation.

Similarly, one of skill looking for the ideal dosage schedule would be able to compare various schedules in parallel without undue experimentation. While the vaccination described in the Examples involves three administrations, the specification explains that the vaccine can also be administered once or twice (*see, e.g.*, page 8, lines 16-19 and page 23, lines 14-22). Pages 14-15 of the specification describe routine methods of monitoring antibody response and cellular immunity.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection under the first paragraph of 35 USC § 112 for enablement.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

Carol Johns

Carol P. Johns
Reg. No. 50,463

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachment: Ex. A
CPJ:cpj
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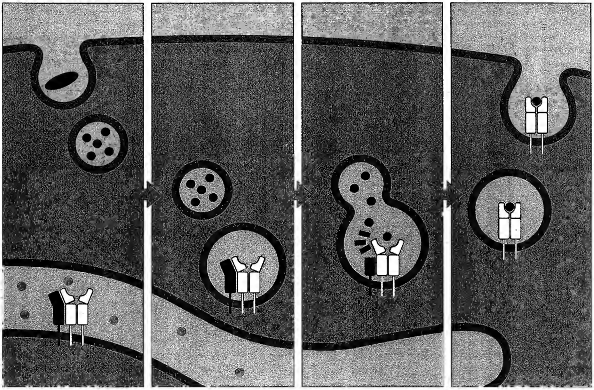
EXHIBIT "A"

IMMUNOBIOLOGY

THE IMMUNE SYSTEM IN HEALTH AND DISEASE



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Distributors
Inside North America: Garland Publishing Inc., 717 Fifth Avenue, New York, NY 10022, USA.
Inside Japan: Nankodo Co. Ltd., 42-6, Hongo 3-Chome, Bunkyo-ku, Tokyo 113, Japan.
Outside North America and Japan: Blackwell Scientific Publications, Osney Mead, Oxford OX2 0EL. Orders to: Marston Book Services Ltd, PO Box 87, Oxford OX2 0DT, UK.
Australia: Blackwell Scientific Publications Pty Ltd., 54 University Street, Carlton, Victoria 3053.

ISBN 0-8153-1497-3 (hardcover) Garland
ISBN 0-8153-1691-7 (paperback) Garland
ISBN 0-86542-811-5 (paperback) Blackwell

A catalog record for this book is available from the British Library.

Library of Congress Cataloging-in-Publication Data
Janeway, Charles.
Immunobiology: the immune system in health and disease/ Charles A. Janeway, Jr., Paul Travers.
p. cm.
Includes bibliographical references and index.
ISBN 0-8153-1497-3 (hardcover). ISBN 0-8153-1691-7 (pbk.).
1. Immune System. 2. Immunity. I. Travers, Paul, 1956- .
II. Title
[DNLM: 1. Immune System--physiology. 2. Immune System--physiopathology. 3. Immunity--physiology. 4. Immunotherapy.
QW 504 1994]
QR181.J37 1994
616. 07'9--dc20
DNLM/DLC
for Library of Congress 94-11058
CIP

This book was produced using Ventura Publisher 4.1 and CorelDraw 3.0.

Printed in Hong Kong by Paramount Printing Co. Ltd.

Published by Current Biology Ltd., Middlesex House, 34-42 Cleveland Street, London W1P 5FB, UK and Garland Publishing Inc., 717 Fifth Avenue, New York, NY 10022, USA.

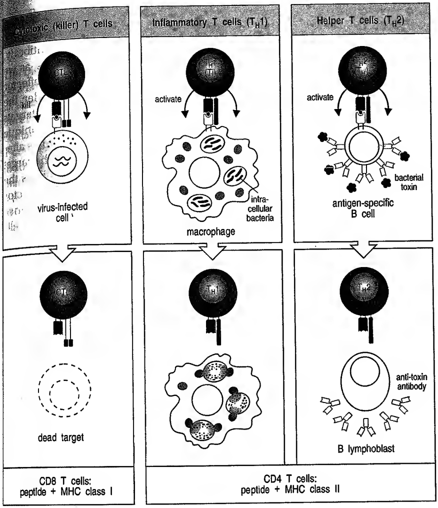

Fig. 7.28 There are three classes of effector T cells, specialized to deal with three classes of pathogens. CD8 cytotoxic cells (left panels) kill target cells that display antigenic fragments of cytosolic pathogens, most notably viruses, bound to MHC class I molecules at the cell surface. Inflammatory CD4 T cells (T_H1; middle panels) and helper CD4 T cells (T_H2; right panels) both express the CD4 co-receptor and recognize fragments of antigens degraded within intracellular vesicles, displayed at the cell surface by MHC class II molecules. The inflammatory CD4 T cells, upon activation, activate macrophages, allowing them to destroy intracellular microorganisms more efficiently. Helper CD4 T cells, on the other hand, activate B cells to differentiate and secrete immunoglobulins, the effector molecules of the humoral immune response.

7-14 Effector T-cell interactions with target cells are initiated by antigen non-specific cell adhesion molecules.

Once an effector T cell has completed its differentiation in the lymphoid tissues it must find the target cells that are displaying the specific peptide:MHC complex that it recognizes. This occurs in two steps. First, the armed effector T cells emigrate from their site of activation in the lymphoid tissues and enter the blood. Second, because of the cell-surface changes that have occurred during differentiation, they migrate into the peripheral tissues, particularly at sites of infection to which they are guided by changes in adhesion molecules expressed on the endothelium of the local blood vessels, as we shall see in Chapter 9.

The initial binding of an effector T cell to its target, like that of naive T cells with antigen-presenting cells, is an antigen non-specific interaction mediated by the LFA-1 and CD2 adhesion molecules. However, the level of LFA-1 and of CD2 is two- to four-fold higher on armed effector T cells than on naive T cells and, therefore, armed effector T cells can bind efficiently to target cells that have lower levels of ICAMs and LFA-3 on their surface than professional antigen-presenting cells. This interaction, again like that of naive T cells with antigen-presenting cells, is normally transient unless specific recognition of antigen on the target cell triggers a change in the affinity of LFA-1 for its ligands on the target-cell surface. This change causes